

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Reports
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[Signature]

Applicant: Nicolas VOUTE *et al.*

Title: SMALL DENSE MICROPOROUS SOLID SUPPORT MATERIALS,
THEIR PREPARATION, AND USE FOR PURIFICATION OF
LARGE MACROMOLECULES AND BIOPARTICLES

Appl. No.: 09/274,014

Filing Date: March 22, 1999

Examiner: D. Sorkin

Art Unit: 1723

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AMENDMENT AND REQUEST FOR RECONSIDERATION

UNDER 37 CFR §1.116

Commissioner for Patents
Washington, D.C. 20231

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In reply to issues raised in the Office Action mailed December 19, 2002, applicants traverse the bases for rejection. Claims 1-66 are pending. Claims 23-58, and 64-66 are withdrawn from consideration. Claims 1-22 and 59-63 are rejected. Claims 1-66 remain in the case.

Claims 1-22, and 59-63 stand rejected under Section 103(a) based on Girot *et al.* (U.S. 5,445,732). The examiner states that

Girot ('732) discloses dense mineral oxide supports comprising a mineral oxide matrix having an external surface and pores; and an interactive polymer network which fills the pores and is coated on the surface of the mineral oxide matrix. Girot ('732) does not explicitly disclose the porosity being 'less than 30% of the total volume of the mineral oxide matrix' as claimed.

However, Girot ('732) recognizes that a broad range of porosities are suitable for the invention [citing col. 8, lines 40-45; col. 15, line 45; and col. 36, lines 12-15]

Girot ('732) discloses, in column 8 that:

Typically, the present invention utilizes base matrices having the following characteristics: an initial average particle size ranging from about 5 to about 1000 microns; an initial porous volume ranging from about 0.2 to about 2 cm³/gram; an initial surface area ranging from about 1 to about 800 m²/gram; and an initial pore size ranging from about 50 to about 6000 angstroms. Preferably, the base matrix is characterized by: an initial average particle size ranging from about 10 to about 300 microns, although passivated supports having narrow particle size ranges, such as about 15-20, about 15-25, about 30-45, about 50-60, about 80-100, and about 100-300 microns, are most preferred. Preferred ranges for other characteristics include an initial porous volume ranging from about 0.8 to about 1.2 cm³/gram; an initial surface area ranging from about 10 to about 400 m²/gram; and an initial pore size ranging from about 1000 to about 3000 angstroms. The density of the porous solid matrix obviously varies with its chemical nature, being higher for mineral oxide (*e.g.*, silica) substrates and lower for polymeric ones (*e.g.*, polystyrene).

The use of pore volumes ranging from 0.8 to 1.2 cm³/gr of solid material marks a fundamental difference between Girot ('732) and the present invention. Girot ('732) relates primarily to porous silica, for which a porous volume of 0.8 to 1.2 cm³/gr equates to a pore volume of between 0.4 to 0.6 ml per ml of solid material or between 40 and 60% (porous silica has a volume/weight ratio of 2, *i.e.*, 2 ml or 2 cm³ of beads yield about 1 gram of material). This is consistent with attestations in Dr. Boschetti's previously-submitted declaration in this case. Dr. Boschetti is a co-inventor of Girot ('732) and thus eminently qualified to inform as to its content. Dr. Boschetti attested that the purpose of invention described in Girot ('732) was to have a hydrogel fill the pores entirely, while allowing even macromolecules still to diffuse inside. Thus, the pore volume was made as large as possible, and the 40 to 60%

calculated above is in line with this purpose.

This also is supported by the disclosure of Girot ('732). At column 19, it is disclosed that:

It is believed, without wishing to be limited by theory, that a highly open, flexible lattice structure comprised primarily of polymeric chains of repeating main monomer units is formed within the pores of the porous solid matrix. Very significantly, it is believed that the areas of the porous support available for desirable reversible interaction with biological molecules are not confined to the regions immediately adjacent to the surface of the pore as is the case when thin, substantially two-dimensional coatings are applied to porous surfaces in the manner of Steuck (U.S. Pat. No. 4,618,533) and Varady et al. (U.S. Pat. No. 5,030,352) as discussed in Section 2.2 above. Rather, it is believed that the polymeric network of the present invention extends outwardly into the pore volume itself in the manner of a three-dimensional lattice, as opposed to a two-dimensional coating limited strictly to the pore wall surface area. A schematic diagram of such a structure, as it is thought to exist, is illustrated in FIG. 5, where a biological molecule of interest (depicted as a spherical object) is also shown interacting with the lattice. Furthermore, the presence of porogens (pore-inducers) in the passivation mixture is believed to promote creation of this open three-dimensional polymer network.

It is thought that perhaps the open, flexible nature of the three-dimensional polymer network allows biological molecules *to rapidly penetrate the polymer lattice and thereby efficiently interact with sorptive groups in the polymer network of the passivated porous support* even at high solution flowrates. The *rapid and efficient mass transfer of biomolecules into and through this network* avoids the decrease in useful or dynamic sorption capacity and resolution that are typical of conventional chromatographic media. With these conventional media, diffusion in the pores of the support and/or materials coated thereupon or within them leads to poor mass transfer rates and limits the efficiency of the chromatographic process.

(Emphasis added)

This approach, in which biomolecules enter the pores of a mineral oxide bead, contrasts sharply with the present invention, in which pore volume is minimized in order to foreclose access to the pore volume by molecules in the solution. The low porosity as presently claimed allows a crosslinked polymer to be stably rooted in the matrix, “so that subsequent interaction with macromolecules occurs on the external surface area of the support.” This is clearly contrary to both the purpose of Girot ('732) and to the physical structure taught by Girot ('732).

The examiner argues that a skilled artisan would have been motivated to minimize porosity in light of Girot's teaching that “it is generally desirable to have as great a density difference as possible between the solid support particles and the fluidizing medium.” This teaching in Girot ('732) must, however, be balanced against the primary purpose of Girot ('732). The primary purpose in Girot ('732) is to provide a bead in which even macromolecules can enter the pores. While a skilled artisan might be motivated to select values at the lower end of the stated pore volume range in Girot ('732) when designing beads for fluidized bed chromatography, in order to maximize the density difference, that skilled artisan would not be motivated to extend the range lower than the endpoint of the disclosed range. Such an extension beyond the range disclosed in Girot ('732) would directly contravene the ability to have biomolecules diffuse into the pores. A porosity of less than 30% as presently claimed is therefore not a “workable” range when considered in light of the purpose of Girot ('732), and one of ordinary skill in the art would not be motivated to use a pore volume less than the endpoint of Girot's range.

In the alternative, claims 1-22 and 59-63 stand rejected under Section 103(a) based on Girot *et al.* in view of Davis *et al.* (U.S. 4,203,772). The examiner relies on Davis ('772) as explicitly disclosing mineral oxide matrixes having porosities less than 30%, and argues that it would have been obvious to use matrix material of Davis ('772) in place of the matrix disclosed in Girot ('732). Once again, this would be contrary to Girot's purpose of providing beads in which biomolecules penetrate “an open, flexible ... three-dimensional polymer network” that is

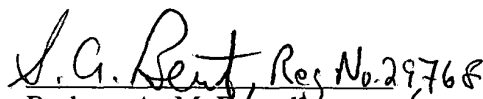
contained in the pores. Interaction in Girot ('732) is not on the surface as presently claimed. To modify Girot ('732) by using the mineral oxide matrix of Davis ('772) would be to render Girot unsuitable for its intended purpose. If a proposed modification renders a prior art invention unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. MPEP §2143.01 and *In re Gordon*, 221 USPQ 1125 (Fed. Cir. 1984)

Based on the foregoing, it is believed that all claims are in condition for allowance. Reconsideration of all rejections and a notice of allowance are respectfully requested. Should there be any questions regarding this application, the examiner is invited to contact the undersigned attorney at the phone number listed below.

Respectfully submitted,

Date June 6, 2003

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